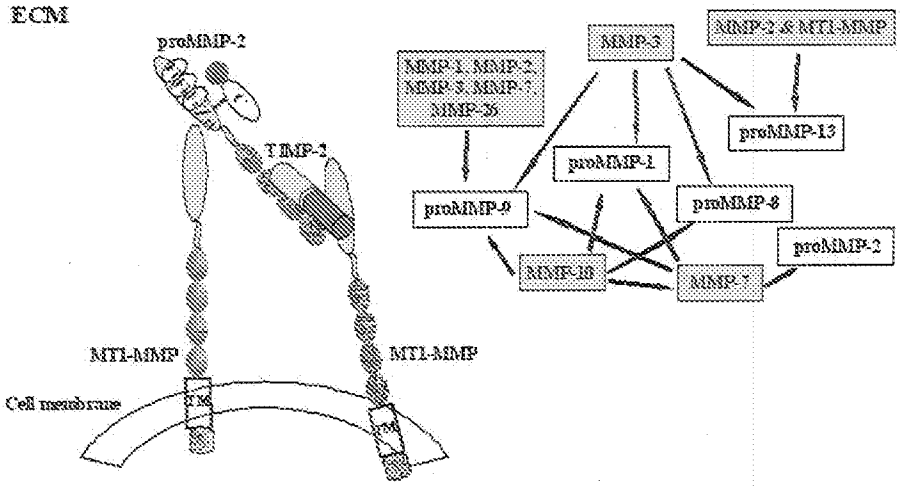
Remarks

Claims 1, 16, 20-24, 26, 27 and 31-34 are pending. Claim 35 has been cancelled. Claims 1, 26, 27 and 33 have been amended. Support for the amendments may be found throughout the specification as filed and, for example, for amended Claim 1 at page 47, lines 22 to 25 and page 48, line 28 to page 49, line 2. The Applicants respectfully request entry of the amendments which are believed to place the application in condition for allowance.

Claims 1, 16, 20-24, 26, 27 and 31-34 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Claims 1, 16, 20-24, 26, 27 and 31-34 satisfy the written description requirement. Reasons are set forth below.

The rejection states that Dr. Al-Jamal's Declaration under §1.132 filed on September 21, 2010 is insufficient to overcome the written description rejection as the Declaration is limited in scope to (i) JB1a, (ii) emphysematous mice, and (iii) inhibiting MMP12 and *in vitro* inhibiting MMP2/9 at 2 and 6 hours. Specifically, the Declaration fails to show the effect of the JB1a antibody on MMP-1, MMP-7, MMP-14, MMP-15, MMP-16 and MMP-26 among others and that it is not clear whether the effect of JB1a is selective to MMP-12, MMP2/9 in PPE-induced emphysema or would act on altering all the metalloproteinases in all tissue repair including emphysema.

The Applicants submit that, while only MMPs-2, 9 and 12 were examined in Dr. Al-Jamal's Declaration, that one skilled in the art would appreciate that regulation of MMPs-2, 9 and 12 results in modulation of the MMP balance because the activation of these metalloproteinases both depends on and results in activation of other MMPs. The dissertation by Heidi Palosaari (2003) (copy enclosed herewith) discloses the cascading nature of MMP activation, that is, MMPs are known to activate each other sequentially (see below figure). Thus, as in the case of caspases mediating apoptosis, those skilled in the art can predict sequential activation on the basis of probing key central MMPs. To that end, although only MMPs-2, 9 and 12 in human primary tissue and cell lines and MMP 12 in animal models were examined in Dr. Al-Jamal's Declaration under §1.132 filed on September 21, 2010, based on the figure below and the known cascading nature of MMPs the Applicants submit that it is reasonable to expect that these MMPs are not the only MMPs activated, but are part of a cascading action involving other MMPs.



MMP activation cascade (Palosaari, 2003)

The Applicants therefore submit that the effect of the JB1a antibody on modulation of MMP balance has been shown and that one skilled in the art would not consider the scope of the Declaration of Dr. Al-Jamal as being limited as set forth in the rejection.

Additionally, the Applicants respectfully disagree with the rejection's position that one skilled in the art would not expect that a clone to the TAEKLK sequence of beta1 integrin would replicate the effects of the JB1a antibody because JB1a is a conformational antibody. The JB1a clone binds to a region of the receptor which is widely known to be linear (see figure below). The epitope mapping which was carried out by Ni and Wilkins utilized the phage display system (Ni and Wilkins (1998), "Cell Adhesion and Communication" (copy enclosed herewith)). They used both synthetic peptides and purified beta1 integrin and determined consensus sequences of TxxKLK, S/GxxKLK and TxxKLR. The first sequence approximated to TAEKLK in beta 1 integrin and the last sequence approximated to TPAKLR of the 179-184 amino acids. However, when binding assays were carried out using JB1a with TAEKLK and TPAKLR, binding occurred only with TAEKLK. Both epitopes are linear and are not known to contain amino acids sequences with any glycosylation. The Applicants therefore submit that one skilled in the art would understand that the JB1a clone binds to a region of the receptor which is linear and that therefore raising another clone to the same sequence will replicate the effect of JB1a binding.

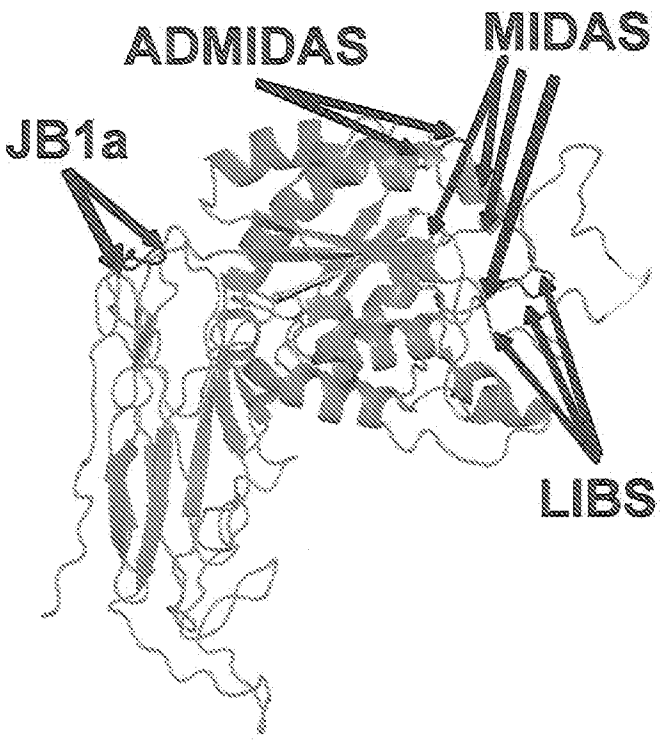


Figure: the location of the JB1a epitope as mapped by Ni and Wilkins produced using polyview 3D as described in http://polyview.cchmc.org/polyview3d.html.

Additionally, the rejection states that although SG/19, which binds within the same region of beta 1 integrin as the JB1a antibody, has been shown to have an effect on MMP9 activity in tumor tissue, the Applicants fail to show that SG/19 has any effect on tissue repair as MMP-9/laminin-5 does not represent the claimed alteration in the MMP balance in the genus of tissue repair. The Applicants submit Tsuji and Saito were brought to the Examiner's attention in response to the assertion that the effect of anti-TAEKLK antibodies on modulation of MMP balance had not been shown. The Applicants are not arguing that the documents of Tsuji and Saito show tissue repair, but that these documents show the effect on MMP balance of an anti-TAEKLK antibody other than JB1a. Moreover, the Applicants are not suggesting that causing any one of the three processes referred to in Claim 1 alone, that is, (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance or (iii) an increase in the anabolism of the extracellular matrix, will induce tissue repair.

Rather, these three processes result from functional modulation of beta 1 integrin and together constitute tissue repair. SG/19 has not yet been shown to induce tissue repair as, as detailed

in the Applicants' response to the Official Action dated January 28, 2010, it is not commercially or widely available. However, the Applicants submit that SG/19 does act in the same manner as JB1a to induce tissue repair as, as discussed above, raising another clone to the 82-87 amino acid region of beta 1 integrin will replicate the effect of JB1a binding as the epitope is linear.

Furthermore, the published work of Luo et al. (1994) (copy enclosed) shows that SG/19 induces the same intermediate conformational state of beta-1 integrin as that induced by the JB1a antibody, as evidenced by the FRET data included in the Declaration under §1.132 filed on December 28, 2009. The Applicants submit that it is this intermediate conformational state of beta-1 integrin which is responsible for the observed tissue repair and the fact that SG/19 has been shown to induce this conformational state is evidence of the utility of SG/19 in tissue repair.

Furthermore, the Applicants submit that it is amino acid residues at the region of amino acids 82 to 87 which mediate the functional modulation of beta-1 integrin required for tissue repair. This is shown by the fact that SG/19 binding within this region induced the same intermediate conformational state of beta-1 integrin as that induced by JB1a (Luo et al., 1994), as discussed above. Thus, because the region of amino acids 82 to 87 is responsible for mediating the functional modulation of beta-1 integrin, whether JB1a may possibly also bind amino acids 179-184 is irrelevant to assessing the properties of SG/19.

For the sake of completeness, it is noted that JB1a only *possibly* binds 179-184 as shown in Ni and Wilkins (1998) where binding assays were carried out using JB1a with TAEKLK and TPAKLR, but binding occurred only with TAEKLK. Furthermore, it is submitted that SG/19 may also bind the minor consensus sequence present in 179-184 given that its epitope major consensus sequence is the amino acids 82 and 87, which are identical to amino acid residues 179 and 184. The Applicants, therefore, submit that there is support that SG/19, and other anti-TAEKLK antibodies which bind to the same linear epitope of beta-1 integrin as JB1a, will replicate the tissue repair effects observed with JB1a.

Furthermore, the Applicants submit that the link between emphysema and other tissue types was described on pages 8 and 9 of the Response to the Official Action filed on September 21, 2010. Furthermore, the Applicants have previously provided working examples for Parkinson's disease, arthritis and Alzheimer's. The Applicants therefore submit that the invention is clearly not limited to

emphysema, but extends to all tissue types wherein degradation of the extracellular matrix has occurred.

Accordingly, the Applicants submit that the specification describes the invention in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the invention. The Applicants respectfully request withdrawal of the written description rejection.

Claims 1, 16, 20-24, 26, 27 and 31-34 are rejected under 35 USC §112, first paragraph, as non-enabled. Claims 1, 16, 20-24, 26, 27 and 31-34 are enabled. Reasons are set forth below.

The Applicants note that the rejection states that the specification is enabling for a method of promoting tissue repair in lung emphysema comprising administering the JB1a antibody or antibodies that bind TAEKLK of SEQ ID NO:1. However, the Examiner has included Claims 26 and 34 which are restricted to lung emphysema in the enablement rejection. Withdrawal of the rejection is requested for these claims which the Applicants understand the Examiner to consider enabled.

The rejection states that at issue is whether or not the claimed anti-TAEKLK antibodies which modulate the function of beta-1 integrin would function to promote any tissue repair and that it is not clear that PPE-induced emphysema would represent all claimed tissue repair. The Examiner states that substantiating evidence may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans.

The Applicants submit that the specification is not limited to emphysema. This is detailed in the specification at, for example, page 46, lines 17 to 19, and page 48, lines 15 to 22, and is substantiated by (i) Dr. Al-Jamal's Declaration under §1.132 filed on December 28, 2009 which contained data demonstrating the JB1a antibody is effective in the treatment of Parkinson's disease (*in vivo* data), arthritis (*in vivo* and *in vitro* data) and Alzheimer's (*in vitro* data) in art accepted models. This is contrary to the rejection's position that the Applicants have no working examples demonstrating an *in vivo* treatment regiment with anti-beta-1 antibodies to promote any tissue repair; (ii) the arguments provided on pages 8 and 9 of the Response filed on September 21, 2010 regarding the lack of compartmentalization of injury in the lung, the effect of COPD on all tissues and the known association between COPD and other conditions; and (iii) the Applicants' comments provided below in response to the rejection's statements regarding the unpredictability of the art.

The rejection states that, for this therapy to be predictable, beta-1 integrin modulation must play a role in all tissue repairs. The Examiner cites Grose and Zweers as presumably examples of art which show that beta-1 integrin modulation does not play a role in all tissue repairs. Grose pertains to the complete deletion of beta-1 integrin, which is not the same as the functional modulation of beta-1 integrin required by the subject matter claimed. In contrast to Grose, the claimed subject matter is neither complete inhibition nor complete activation of beta-1 integrin and which, unlike Grose, does not affect the overall expression level of beta-1 integrin. Secondly, although re-epithelialization eventually occurred, it was largely abnormal with compromised tensile strength, as discussed in page 2312, paragraph 3. Thus, complete inhibition of beta-1 integrin resulted in abnormal remodelling rather than repair. This does not indicate that beta-1 integrin modulation does not play a role in all tissue repairs.

Zweers was focused on the alpha-2 molecule of the alpha-2 beta-1 integrin heterodimer. Thus, Zweers discloses that alpha-2 is dispensable for re-epithelialization, but does not teach that all beta-1 integrin receptor types are indispensible for re-epithelialization. Beta-1 integrin was neither manipulated nor altered and the teachings of Zweers are, thus, not related to the subject matter claimed. The Applicants therefore submit that neither Grose nor Zweers show that beta-1 integrin modulation does not play a role in all tissue repairs. These documents therefore do not show that the subject matter claimed is unpredictable.

The rejection also queries whether (i) anti-TAEKLK antibodies are selective to specific MMPs or generic to all MMPs and (ii) do the anti-TAEKLK antibodies act as inhibitors and activators of MMPs in concert with the type of tissue repair so that the balance of the inhibition/activation of one MMP or all MMPs counts. In response, the Applicants refer the Examiner to the above discussion regarding the cascading activation of MMPs, which entails lack of association. It is the anti-TAEKLK effect on the cell behavior itself which in turn normalizes MMP activity to that usually present at its physiological baseline. This explains the wide spectrum of indications in which beta-1 integrin targeting has been shown to have efficacy.

The Applicants submit that the methods in the description detail the target, that is, the TAEKLK sequence of beta1 integrin. Those skilled in the art would be able to produce an antibody which binds to this region without undue experimentation. Furthermore, the specification details the biomarkers which can be used to confirm functional modulation of beta 1 integrin as required by

Claim 1, namely (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance and (iii) an increase in the anabolism of the extracellular matrix (for example, page 35, line 20 to page 36, line 2 of the specification). These biomarkers can be easily measured by one skilled in the art using commercially available reagents and kits, for example, apoptosis can be measured using TUNEL assay or caspase activity as widely known and accepted, MMPs activity is amenable to simple ELISA type assays which are widely available, and extracellular matrix production could be measured using techniques such as Western Blotting or Immunohistochemistry, both of which are available for small scale detection and high throughput platforms such as those using systems such as AQUA system (HistoRx.com).

In view of the above, the Applicants submit that one of ordinary skill in the art could readily carry out the method of the claimed invention without undue experimentation for tissue repair of any tissue type. The Applicants respectfully request withdrawal of the enablement rejection.

Claims 1, 16 and 20-24 are rejected under 35 USC §102(b) as being anticipated by US Patent No. 2003/0109435, as evidenced by the Al-Jamal Declaration and Chemicon International catalog no. MAB1965. The rejection states that when a claimed process is not directed to a new use, consists of the same steps described in a prior art reference, and the newly discovered results of the known process directed to the same purpose are inherent, the process is not patentable.

The Applicants submit that the steps of the claimed process are not the same as the steps described in US '435 as the claimed process comprises the step of administering the anti-TAEKLK antibody to a tissue wherein the cells are undergoing cell death whereas US '435 teaches administration of the JB1a antibody at an earlier stage where the cells are not yet undergoing cell death. Specifically, US '435 teaches administration of the JB1a antibody to inhibit formation of amyloid deposits.

Formation of amyloid deposits in neurons takes place before cell death, as evidenced by Kadowaki et al. (2005) and Morishima et al. (2001) (copies enclosed), which show that cell death is caused by, and therefore subsequent to, formation of the amyloid deposits. US '435 teaches administration of the JB1a antibody to inhibit formation of amyloid deposits and, as such, it necessarily teaches administration of the JB1a antibody at an earlier stage than when the cells are undergoing cell death as, based on the teachings of US '435, administration of the JB1a antibody would not be beneficial once the cells are undergoing cell death as at that stage amyloid formation

has already occurred. The Applicants therefore submit that US '435 does not disclose the Applicants' claimed subject matter as US '435 does not teach administration of the JB1a antibody to a tissue undergoing cell death.

The Examiner further states that although US '435 is silent with regard to the JB1a resulting in (i) inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance and (iii) an increase in the anabolism of the extracellular matrix, as claimed in Claim 1, a compound and all of its properties are inseparable. Therefore, in the absence of evidence to the contrary, the JB1a administered would be expected to result in the claimed properties.

In response, the Applicants submit that there is evidence in US '435 which shows that the claimed properties of JB1a were not present in US '435. Specifically, no cell death was indicated in US '435 either in the pictures or in the description. If cell death had occurred, it would have been evident in the pictures of US '435. However, in US '435, the morphology which is characteristic of apoptosis (cell shrinkage and rounding, dense cytoplasm and tightly packed organelles, pyknosis, karyorrhexis, irregular blubbling of cell membrane and presence of apoptotic bodies) is absent. Therefore, US '435 does not disclose cell death, either expressly or inherently. In the absence of the presence of cell death, US '435 cannot inherently or otherwise disclose inhibition of apoptosis. To inherently anticipate, the prior art must necessarily function in accordance with, or include, the claimed limitations. The Applicants therefore submit that US '435 does not inherently disclose the Applicants' claimed subject matter as the claimed properties of JB1a were not present in US '435.

The Applicants further submit that US '435 does not make obvious the claimed subject matter for the following reason. US '435 entails the use of non-terminally differentiated cells derived from fetal brain tissues, which normally proliferate. This is in stark contrast to adult and/or terminally differentiated neurons which do not normally proliferate. In fact, as shown in the attached review by Herrup et al. (2004) (copy enclosed), it was known at the time of filing US '435 that inducing proliferation of mature neurons has been shown to induce neuronal cell death. US '435 teaches that targeting beta 1 integrin in fetal neurons resulted in the neurons regaining proliferative potential. However, one skilled in the art would be aware that inducing proliferation of mature neurons would be harmful. As such, US '435 teaches away from administration of the JB1a antibody to mature neurons. The finding of the Applicants' claimed subject matter that the JB1a

antibody actually inhibits cell death is therefore surprising in light of the teaching of US '435 that the JB1a antibody induces proliferation of fetal neurons.

The Applicants respectfully request withdrawal of the rejection made in view of US '435.

Claims 1, 16 and 20-24 are rejected under 35 USC §102(b) as being anticipated by US Patent No. 6,123,941.

The rejection states that US '941 teaches methods for reversing malignant phenotype as the use of the JB1a antibody to reverse extracellular matrix remodelling and promoting tissue repair can include reversing malignant phenotype. Thus, US '941 reads on the claimed method of promoting tissue repair. The Examiner submits that malignant phenotype indicates that the extracellular matrix has been degraded via MMPs and/or cathepsins.

In response, the Applicants submit that promoting tissue repair by administering an antibody to a tissue undergoing cell death, wherein extracellular matrix of the tissue has been degraded does not include reversing malignant phenotype. Regenerative medicine involving tissue repair is known to be a separate field to cancer as shown in the following references: http://en.wikipedia.org/wiki/Regeneration_(biology), http://en.wikipedia.org/wiki/Regenerative_medicine and Beachy et al. (2004) (copies enclosed). Furthermore, malignant tissue is not be considered a tissue undergoing cell death. The Applicants therefore submit that the Applicants' claimed subject matter does not include reversing malignant phenotype.

Furthermore, the Applicants submit that the Applicants' claimed subject matter would not have been obvious in light of US '941. The US '941 inventors have described the effect of beta 1 integrin inhibition on normal cells to be pro-apoptotic, which is in contrast to what is required to ensue tissue repair.

The Applicants respectfully request withdrawal of the rejection made in view of US '941.

Claims 1 and 20 stand rejected under 35 USC 103(a) as being obvious over US '941 in view of Owens.

The deficiencies of US '941 are discussed above. Owens does not remedy these deficiencies.

The Applicants therefore respectfully request withdrawal of the rejection made in view of US '941 and Owens

Claims 1, 16, 20-24 and 31 stand rejected as being unpatentable over US 2007/0048321 in view of Chen. The rejection states that US '321 teaches a method for treating fibrosis comprising administering a pharmaceutical composition comprising an antibody molecule comprising antigen binding regions of an antibody to an integrin wherein the antibody is selected from a group including an anti-beta 1 antibody. As acknowledged by the rejection, US '321 does not teach an antibody that binds to the beta 1 integrin molecule at residues TAEKLK. However, the rejection states that Chen discloses the use of functional-blocking mAbs such as JB1a against various integrins. The Examiner submits that those skilled in the art would have had reason to use the functional blocking mAb JB1a of Chen in the method of US '321 to target beta 1 integrin.

The Applicants submit that US '321 and Chen relate to fibrosis. In fibrosis, there is an abnormal increase in matrix anabolism. Thus, treatment of fibrosis differs from the Applicants' claimed subject matter where administration of the antibody to a tissue increases anabolism of the extracellular matrix. Accordingly, one skilled in the art would not look to US '321 or Chen in developing a method of promoting tissue repair comprising administering an antibody, which modulates function of beta 1 integrin, to a tissue undergoing cell death which results in (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance and (iii) an increase in the anabolism of the extracellular matrix. US '321 and Chen actually teach away from the claimed subject matter because they teach that inhibition of beta 1 integrin will reduce matrix anabolism, whereas increased matrix anabolism is required in tissue repair.

Furthermore, US '321 describes the use of a beta 1 integrin antibody targeting a sequence in the beta A domain (that is, the I-like domain) and, more specifically, the MIDAS region. This is distinct from the TAEKLK sequence in the hybrid region targeted by JB1a. Chen merely describes disruption of the binding of integrins to their ligands using JB1a. Chen, in fact, highlights the importance of activation of metalloproteinases and the interaction of connective tissue growth factor (CTGF) with beta 1 integrin during angiogenesis and wound healing. Chen, therefore, further teaches away from the claimed subject matter because it teaches that inhibition of the interaction between CTGF and beta 1 integrin would be detrimental to tissue repair.

The Applicants therefore respectfully submit that Claims 1, 16, 20-24 and 31 are not obvious in view of US '321 and Chen and request reconsideration and withdrawal of the rejection.

Claims 1, 16 and 20-24 and 31 stand rejected as being unpatentable over US 6,251,419 in view of Weigel-Kelley. The rejection states that US '419 teaches a method for controlling tissue regeneration of the periodontium comprising applying a first antibody which binds to an alpha chain and a second antibody which binds to an integrin beta chain, wherein either the first antibody binds to the alpha-6 subunit and/or the second antibody binds to the beta-1 subunit. As acknowledged by the rejection, the '419 publication does not teach an antibody that binds to the beta 1 integrin molecule at residues TAEKLK. However, the rejection states that Weigel-Kelley teaches use of JB1a antibodies as beta-1 function blocking antibodies and that one skilled in the art would have been motivated to use the functional-blocking anti-beta-1 antibody JB1a of Weigel-Kelly in the method disclosed in US '419 because, like the compounds taught in US '419, the JB1a antibody is a beta-1 integrin function-blocking antibody.

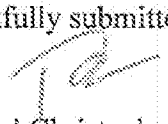
The Applicants submit that Weigel-Kelley teaches that the addition of anti-integrin antibodies was shown to inhibit epithelialization of marginal gingival biopsies comprising epithelium and sub-epithelium connective tissue (page 3, left column, lines 50-55). Epithelialization is a key component of wound healing or wound closure. Weigel-Kelley therefore teaches away from the claimed subject matter because it teaches that inhibition of beta-1 integrin would in fact be detrimental. Furthermore, P4C10 binds the 207-218 amino acid sequence of the beta A domain.

The Applicants therefore respectfully request withdrawal of the rejection made in view of US '419 and Weigel-Kelley.

Claims 1, 16, 20-24, 27 and 31-34 stand provisionally rejected on the ground of nonstatutory double patenting over Claims 1, 2, 5, 11, 16, 19, 24, 25, 32, 35, 57 and 59-63 of copending US Application No. 12/528,749. The Applicants respectfully submit that because the rejection is provisional, they will address it when the rejection becomes non-provisional.

In light of the foregoing, the Applicants respectfully submit that the application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,



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